Acute coronary syndrome and renal impairment: a systematic review

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Abstract

Background: Coronary artery disease (CAD) and chronic kidney disease (CKD) may reciprocally influence each other. Patients with CAD and CKD have an increased risk of both ischemic and hemorrhagic events. **Methods**: In the present review, we summarize the existing literature focusing on the relationship between kidney dysfunction and acute coronary syndromes (ACS) in terms of risk factors, complications, and prognosis. We discuss also about the best evidence-based strategies to prevent deterioration of renal function in patients with CAD. **Results**: Patients with CKD less frequently receive an invasive management (percutaneous or surgical revascularization) and potent antithrombotic drugs. Nevertheless, recent evidence suggests they would benefit from a selective invasive management, especially in case of ACS. **Conclusion**: Patients with CKD and CAD represent a challenging population, more randomized controlled trials and meta-analyses are needed to better define the best therapeutic strategy during an ACS episode.

Keywords: acute coronary syndromes; chronic kidney disease; acute kidney injure; coronary artery disease; revascularization

1. Chronic kidney disease as risk factor of acute coronary syndrome

The prevalence of chronic kidney disease (CKD) in the general population stands at 13% and increases to 20–25% in patients with acute coronary syndrome (ACS) [1]. CKD is an independent risk factor for cardiovascular events often consisting in pauci-symptomatic clinical presentation and atypical elettrocardiogram (ECG) changes, making the diagnosis of ACS more challenging.

It has been observed that as renal function decreases, cardiovascular risk progressively increases. Indeed, patients with renal dysfunction are most likely to present an acute myocardial infarction (AMI) [2] with an even higher prevalence of ACS in dialyzed patients. Indeed, chronic inflammation, hyperhomocysteinemia and oxidative stress leading to endothelial dysfunction, coronary artery calcification, as well as the use of immunosuppressants have all been associated with accelerated atherosclerosis and coronary events [3]. Periodic exposure of blood to the dialysis membrane may also induce platelet reactivity (PR), which leads to an increased risk of ischemic events and resistance to anti-thrombotic treatment in dialyzed patients [4,5].

2. Acute kidney injury

According to the Acute Kidney Injury (AKI) Network, AKI is defined as an absolute increase in serum creatinine

(sCr) of 0.3 mg/dL or greater, or as an increase to 1.5-fold or greater from baseline. This definition was adopted by the universal guidelines developed by the KDIGO (Kidney disease–Improving global outcome) organization and is currently the most frequently used for any cause of acute renal injury [5].

A further definition has been proposed in the context of AKI relating to contrast media used during percutaneous coronary intervention (PCI). It is based on absolute increase in sCr level of at least 0.5 mg/dL (44 microMol/L) within 48–72 hours after contrast exposure or as a relative increase in sCr of >25% [6].

Several factors, such as parenchymal ischemia, direct and indirect tubular or endothelial damage, contribute to the development of contrast induced-AKI [7]. Contrast medium (CM) induces an increase in viscosity in the renal tubule leading to renal hypoperfusion through the constriction of the vasa recta [8]. Specifically, the CM-induced hypoxic damage afflicts both medullary and cortical regions, with a consequent reduction of estimated glomerular filtration rate (eGFR) and a concomitant tubular damage. The increase of reactive oxygen species and the reduction of nitric oxide leads to renal vasoconstriction ultimately resulting in additional tubular as well as endothelial damage. This effect varies according to the osmolarity and the viscosity of the CM, with maximum damage produced by high osmolarity iodine-based contrast agent (HOCM). Furthermore,

HOCM influences the shape of the erythrocytes, causing difficulties in the passage inside the vasa recta with consequent hypoxia of the medullary region [8–11].

The most important risk factor associated with contrast induced-AKI is a pre-existing renal dysfunction [5]. The risk of contrast induced-AKI becomes clinically evident when the baseline sCr concentration is >1.3 mg/dL (>115 mmol/L) in men and >1.0 mg/dL (>88.4 mmol/L) in women, equivalent to an eGFR <60 mL/min/1.73 m^2 [12]. Other risk factors for developing contrast induced-AKI include diabetes mellitus (DM), hypertension, heart failure, advanced age, volume depletion, hemodynamic instability, myeloma, use of concurrent nephrotoxic medications, and large volume or high osmolality of the CM [13,14]. Based on this evidence, several predictive models have been identified in order to help reducing the risk of developing contrast induced-AKI after PCI with preventive targeted therapy, guiding the decision making process, and avoiding additional renal insults [5]. Specifically, pre- and post-contrast exposure models and biomarkers were proposed for contest induced-AKI prediction [14–18].

Fundamental strategies to prevent and treat contrast induced-AKI are directed to restore circulatory volume. High osmolarity of CM and increased viscosity may be mitigated with adequate hydration to reduce the CM concentration. To date several hydration strategies have been developed. In the POSEIDON trial, a left ventricular end diastolic pressure guided fluid administration resulting in a significant reduction of contrast induced-AKI compared to usual care [15]. Another strategy is based on the use of the RenalGuard® System in which the losses due to an infusion of furosemide (0.25 mg/kg) are counterbalance by an equivalent intravenous infusion of saline solution. In the REMEDIAL II trial, the use of the RenalGuard® System led to a reduction of the incidence of contrast induced-AKI [16].

The European guidelines recommend using pre-procedure infusion of isotonic solution starting 12 hours before the angiography, and continuing for at least 24 hours afterwards, in order to reduce the risk of contrast induced-AKI, especially if eGFR is <40 mL/min/1.73 m^2. Pretreatment with high dose of statin in statin-naive patients is also recommended [19–21]. Based on the correlation between high osmolarity and incidence of contrast induced-AKI, iso-osmolar CM could lead to a benefit in terms of kidney damage, however conflicting data emerge from the literature [22,23].

Although the use of adequate hydration remains the cornerstone for prevention of the development of contrast induced-AKI, great attention has been placed on trying to minimize the volume of the CM. In this regard, several strategies have been developed, including the use of automatic systems for the injection of the contrast medium, such as: ACIST CVi® (ACIST Medical Systems, Eden Prairie, MN, USA), MEDRAD® Avanta system (MEDRAD Inc.,

Warrendale, PA, USA) and the AVERT™ system, followed by the second-generation DyeVert™ systems (Osprey Medical, Minnetonka, MN, USA). In the AVERT trial, AVERT™ system, in spite of having demonstrated a decrease in the volume of CM compared to traditional methods, failed to accomplish a reduction in the incidence of contrast induced nephropaty (CIN), suggesting that the obtained reduction in the volume of CM that had been obtained was not sufficient to reduce the incidence of AKI [24]. The DyeVert™ system has been recently assesed in a retrospective analysis [25] of 112 patients with ACS undergoing primary PCI: use DyeVert resulted in lower contrast media used (130 [120–188] mL vs. 99 [69–136] mL; $p < 0.001$) and lower incidence of contrast induced AKI (odds ratio [OR] = 0.37; 95% confidence interval [CI] 0.14–0.95; $p = 0.047$) compared to propensity score matched controls. An ongoing trial (ClinicalTrials.gov Identifier: NCT04714736) is assessing DyeVert™ system in ACS setting.

Several studies have focused their attention on PCI not guided by angiographies [26]. One of these, the MOZART trial, shows how ultrasound-guided PCI is effective in reducing the requirement of CM. In another study a total of 31 patients with advance CKD (eGFR <30 mL/min/1.73 m^2) who underwent an elective PCI with zero contrast media were analyzed. A minimal contrast coronary angiogram was first performed followed by a real time intravascular ultrasound (IVUS)-guided zero contrast PCI (no earlier after 7 days of the angiography). There were no major adverse cardiovascular events or CIN [27]. However, further trials are needed to verify the effective ability of this imaging-guided PCI strategy to reduce the incidence of CIN [28,29].

3. Impact of chronic kidney disease in ACS patients

Approximately 25% to 30% of all ACS patients presents at least moderately reduced renal function [30,31]. Noninvasive estimation of renal function is mandatory in every patient with confirmed or suspected ACS admitted to the hospital [32]. Reduced renal function and CKD affect every stage of diagnostic and therapeutic pathway of ACS, with an important prognostic relevance.

4. CKD and diagnosis of ACS

High-sensitivity cardiac troponins (hs-cTn) are the best available biomarkers for early diagnostic of ACS but in CKD patients they are chronically elevated, limiting their clinical usefulness [31,33]. In a retrospective study, 3295 patients presenting chest pain were classified in subgroups based on age, sex and renal function. AMI was diagnosed in 84% of the patients and hs-cTn levels were compared between AMI and non-AMI patients in all subgroups. Optimal cut-offs values of high-sensitivity cardiac troponin I (hscTnI) for diagnosis of AMI in CKD (eGFR <60 mL/min/1.73 m^2) were higher in males than females,

and specificity of 100% was reached in all groups, except in males over 60 years old with severe eGFR reduction ($<$15 mL/min/1.73 m^2) [34]. Despite the lower specificity of hs-cTn in CKD patients, a threshold of $<$5 ng/L may rule out myocardial injury in this population [32,33,35].

5. Prognostic impact of CKD in ACS patients

CKD may worsen the short and long-term prognosis of patients admitted for ACS (Fig. 1). Patients with moderate and severe CKD showed significantly increased risk of hospitalization, mortality and major bleeding episodes (Table 1, Ref. [2,30,36–42]). In the HORIZONS-AMI study, patients with CKD and ST-segment elevation myocardial infarction (STEMI) treated with PCI showed higher risk of mortality, stroke, mayor adverse cardiac events (MACE), and net adverse clinical events (NACE) and non-coronary artery bypass surgery (CABG) related bleeding at 3 years, compared with patients without CKD. Notably, the mortality rate in patients with advanced CKD (creatinine clearance [Crcl] $<$30 mL/min) reached 53% [13]. Impact of renal dysfunction in the elderly was evaluated in 1904 patients from 75 years and over presenting with ACS. Patients were classified in three groups based on the eGFR: $\geq$60, 30–59 and $<$30 mL/min/1.73 m^2. For hospitalized patients, mortality was 1.1%, 2.1% and 4.4% (p = 0.015) while after discharge, all-cause mortality was 3.4%, 5.2% and 12.8% ($p <$ 0.001), respectively [36]. Recurrence of non-fatal myocardial infarction (MI) disabling stroke and bleeding was similar between CKD and no-CKD groups. Patients with eGFR less than 30 mL/min/1.73 m^2 were older, hypertensive, diabetic, with peripheral artery disease, multivessel coronary disease artery, with heart failure with reduced ejection fraction and with anemia [36].

6. CKD and therapeutic options in ACS

Patients with CKD have been frequently excluded from ACS trials [37]. While the decision-making for patients admitted with ACS ST-elevation requires invasive revascularization when feasible, managing patients with ACS without persistent ST-elevation with CKD is challenging for a lack of evidence. In a retrospective analysis from SWEDEHEART data, the incidence of coronary revascularization and its effect on mortality were evaluated in 23,262 ACS patients aged $\leq$80 years. Rates of coronary angiography and invasive revascularization were low in patients with a reduced renal function. For instance, in the severe eGFR reduction/dialyzed group, only 12% of patients underwent PCI and only 3% received coronary artery bypass graft (CABG). An improvement of 1-year survival was observed in patients with mild-to-moderate CKD (eGFR $>$30 mL/min/1.73 m^2) treated with early revascularization (within 14 days of admission). Less benefits and a trend toward harm were observed in the lower renal function group (eGFR $<$30 mL/min/1.73 m^2) [38]. Current guidelines for non-ST- elevation myocardial infarction (NSTEMI) recom-

mend, with a class of evidence IIa/level B, surgical revascularization over PCI in patients with moderate to severe CKD with multivessel coronary disease, a high surgical risk profile and a life expectancy of $>$1 year [32]. This recommendation is based mostly on old data from previous generation of stent and antithrombotic treatments.

A more recent retrospective study from the SWEDE-HEART registry included ACS patients $>$80 years with CKD, defined as an eGFR $<$60 mL/min/1.73 m^2, hospitalized in Sweden from 2011 to 2014. Cox regression was used to estimate all-cause mortality in patients with PCI versus conservative treatment, classified according to the eGFR. Patients invasively treated had a lower risk of death in all groups of eGFR, underling the benefit of this strategy. Higher bleeding events with PCI were observed only in the group of patients with eGFR 15 to $<$30 mL/min/1.73 m^2 [39].

A meta-analysis of comparative studies carried out between 1995 and 2010 analysing the effect of early revascularization in patients with NSTEMI and CKD, showed interesting benefits from early revascularization on short- and long-term mortality. Specifically, a reduction in 1-year mortality compared to initial medical therapy (OR = 0.46, 95% CI 0.26–0.82, p = 0.008) among ACS patients with eGFR $>$60 mL/min/1.73 m^2 was observed. In addition, the effects of 1-year mortality reduction were also observed, after early revascularization, in patients with moderate and severe CKD and end-stage renal dysfunction (ESRD). Although patients with ESRD (39.8%) had a higher risk of 1-year all-cause mortality than those with at least moderate CKD (25.1%), the first group presented a higher absolute risk reduction in 1-year mortality with early revascularization compared to the second one (21.3% vs. 16.6% respectively). These results confirm that the sickest patients could have more benefits from early revascularization [43]. Even though revascularization in this group of patients would be conceptually beneficial, it should be emphasized that most of the evidence derives from registries and meta-analysis. Therefore, further and larger studies are needed to confirm the clinical benefits of the invasive strategy in ACS patients with CKD [44].

The Academic Research Consortium for High Bleeding Risk (ARC-HBR) recognizes severe or end-stage CKD (eGFR $<$30 mL/min/1.73 m^2) as major risk factor for bleeding [45]. On the other hand, as previously discussed, CKD has an elevated ischemic risk. However, neither eGFR nor serum creatinine level were included in DAPT score as ischemic risk score for prolonged dual antiplatelet therapy (DAPT).

DAPT is highly recommended in ACS patients to improve outcome and prognosis, regardless of renal function. However, the efficacy and safety of antithrombotic drugs with potent P2Y12 inhibitors, a chemoreceptor for platelets released adenosine diphosphate (ADP), in patients with severe CKD or ESRD are not clearly evaluated, since
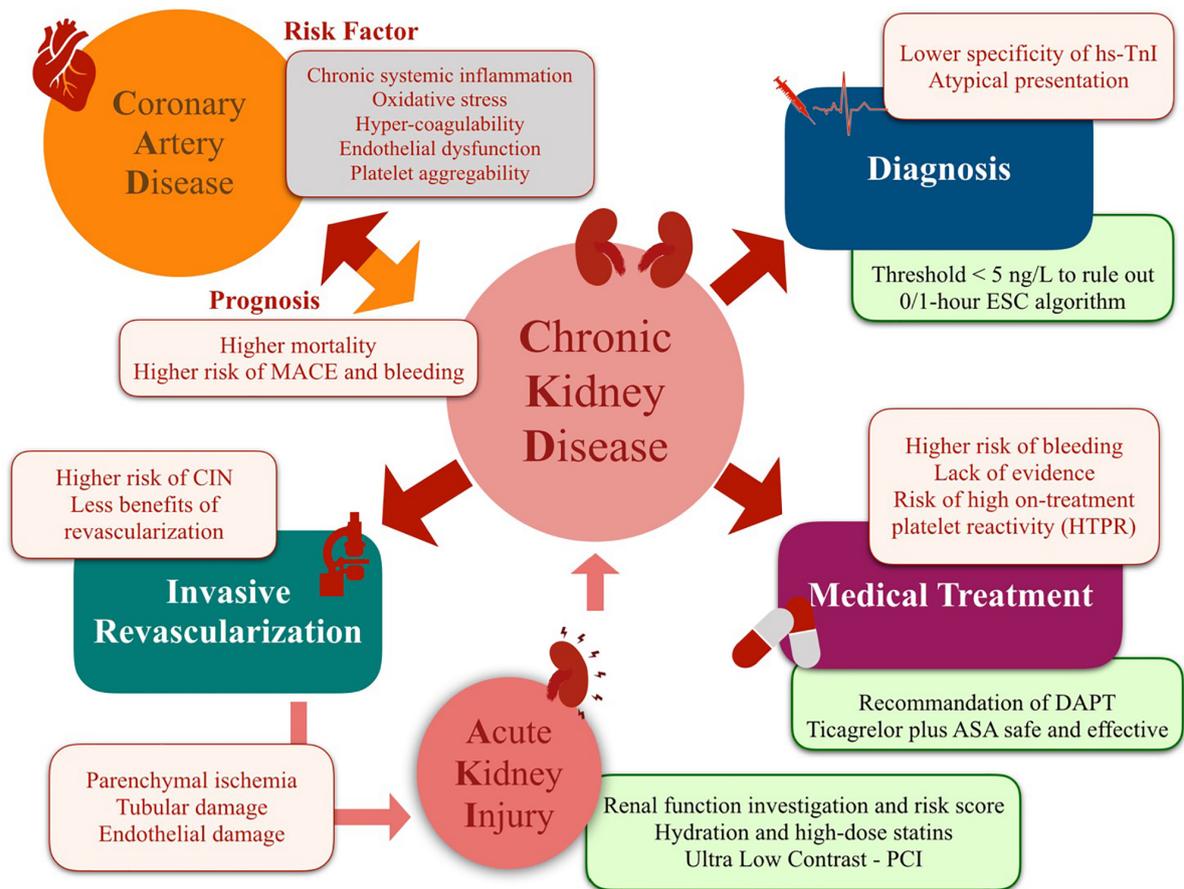
Fig. 1. Kidney dysfunction and acute coronary syndrome.

these patients are frequently excluded from randomized controlled trials [46]. In patient with ACS and CKD there are no contraindications for aspirin, no dose adjustment is required if renal function is reduced [47,48]. Clopidogrel is a prodrug and need activation to bind the ADP receptor. Standard dose of clopidogrel has a lower inhibition of ADP-induced platelet aggregation (–25%) in patients with depressed renal function, and is associated with greater prevalence of high on-treatment platelet reactivity (HTPR), leading to an increased ischemic risk [49,50]. In the ARTIC study, 2440 patients were randomized before drug-eluting stent implantation, both using a strategy of platelet function monitoring and without monitoring. In the monitoring group, 35% of patients had high platelet reactivity (HPR) to clopidogrel [51]. Patients with CKD have a higher risk of HTPR, with an increased rate in lower renal function groups. However, after multivariable adjustment, no significant association was detected between HTPR and CKD, suggesting that risk factors account for HPR in patients with renal impairment [52]. Post hoc analyses of CREDO trial (Clopidogrel for the Reduction of Events During Observation) show a limited efficacy, defined as death, myocardial infarction or stroke, and higher risk of bleeding, after 1 year of clopidogrel vs. placebo in patients with mild to moderate CKD [52]. Similar findings were observed in other analy-

ses [53,54]. Several studies show the superiority of potent oral P2Y12-ADP receptor antagonists, ticagrelor and prasugrel, over clopidogrel in CKD patients [55–58]. Despite the clinical benefits of potent P2Y12-ADP receptor antagonists over clopidogrel in patients with ACS [59,60], clinical and therapeutic experience with prasugrel and ticagrelor is limited in patients with renal impairment (including patients with ESRD).

In the subgroup analysis of the TRITON TIMI 38 trial, including 1490 patients with a eGFR <60 mL/min/1.73 m^2, the benefit of prasugrel over clopidogrel was constant across the the overall population. However, there are no specific data regarding bleeding end point in patients with CKD, but, in the overall trial population, prasugrel increased the rate of major non-CABG related Trombolysis in Myocardial Infarction (TIMI) bleeding [59]. In the PROMETHEUS registry, 19,832 patients ACS patients undergoing PCI under clopidogrel or prasugrel have been included (28.3% with a creatinine clearance <60 mL/min). After propensity adjustment, prasugrel did not confer significant benefit compared to to clopidogrel with respect to the incidence of a composite of end point including death, MI, stroke, and urgent revascularization at 1 year in the CKD subgroup, with a similar rate of bleedings [40].

Table 1. Studies showing impact of kidney dysfunction in acute coronary syndrome.

Authors	n	Aims and groups	Primary endpoint	Secondary endpoints
Go *et al.* [2], 2004	1,120,295	Correlation between the GFR and risks of death, CV events, and hospitalization.	HR for death: 1.2 (95% CI 1.1–1.2), 1.8 (95% CI 1.7–1.9), 3.2 (95% CI 3.1–3.4), and 5.9 (95% CI 5.4–6.5), inversely related to GFR.	HR for Any Hospitalization: 1.1 (95% CI 1.1–1.1), 1.5 (95% CI 1.5–1.5), 2.1 (95% CI 2.0–2.2), and 3.1 (95% CI 3.0–3.3), respectively.
		Results related to group of eGFR (45–59, 30–44, 15–29, and <15 mL/min/1.73 m^2).	HR for MACE: 1.4 (95% CI 1.4–1.5), 2.0 (95% CI 1.9–2.1), 2.8 (95% CI 2.6–2.9), and 3.4 (95% CI 3.1–3.8), respectively.	
Fox *et al.* [30], 2012	59,970 (100% with ACS)	To examine in-hospital all cause death and major bleeding in patients with AKI in setting of MI.	In-hospital all-cause death.	Crude rates of major bleeding: mild AKI 16.5%, moderate AKI 22.6% and severe AKI 32.7%.
		Classification as absolute change in sCr: mild (sCr 0.3–0.5 mg/dL), moderate (SCr 0.5–1.0), and severe AKI (SCr ≥1.0).	OR: 2.4 (95% CI 2.0–2.7) for mild AKI; 4.5 (95% CI 3.9–5.1) for moderate AKI; 12.6 (95% CI 11.1–14.3) for severe AKI.	
De Rosa *et al.* [36], 2020	1904 (100% with ACS)	Correlation between contrast induced-AKI and adverse one-year outcome in elderly patients (mean age 81.0 ± 4.6 years). Stratification according to eGFR (59–30; 30–15; <15 mL/min/1.73 m^2).	Risk of all-cause mortality at 12 months: 4.5%, 7.5% and 17.8% inversely related to GFR (*p* < 0.001).	Severe contrast induced-AKI is associated with a higher risk of all-cause (HR 2.86, 95% CI 1.52–5.37, *p* = 0.001) and CV death (HR 3.11, 95% CI 1.41–6.83, *p* = 0.005).
			Risk of CV mortality at 12 months: (2.8%, 5.2% and 10.2%, respectively).	Contrast induced-AKI incidence significantly higher in STEMI vs. NSTEMI (11.7% vs. 7.8%, *p* = 0.036).
Charytan *et al.* [37], 2006	154,692 (100% with ACS)	To indagate use of coronary angiography (CA) and PCI in patients with CKD (n = 8957) dialysis (n = 2369).	Rate of CABG or PCI was 19.2% in dialyzed patients, 23.0% in patients with CKD, and 41.4% in control group (RR 0.46 [95% CI 0.42–0.52] and 0.56 [95% CI 0.53–0.59] respectively).	Rate of CABG or PCI after CA was 46.4% (RR 0.66, 95% CI 0.61–0.72) in dialysis patients, 61.6% (RR 0.88, 95% CI 0.86–0.90) in patients with CKD, and 70.1% in control group.
			Rates of diagnostic CA were 38.6% in dialyzed patients (RR 0.68, 95% CI 0.64–0.73), 34% in patients with CKD (RR 0.62, 95% CI 0.59–0.64) than in control (56.6%).	
Szummer *et al.* [38], 2009	23,262 patients (100% with NST-ACS)	To investigate 1 year outcome after early invasive management in NSTEMI patients with CKD.	No benefit for PCI in advanced CKD (eGFR <15 mL/min/1.73 m^2) or in dialysis (HR 1.61, 95% CI 0.84 to 3.09, *p* = 0.15).	Rate of patients treated invasively with declining renal function: from 62% with eGFR ≥90 mL/min/1.73 m^2, to 15% with eGFR <15 mL/min/1.73 m^2 or in dialysis, (*p* < 0.001).

Table 1. Continued.

Authors	n	Aims and groups	Primary endpoint	Secondary endpoints
Holzmann *et al.* [39], 2020	12,821 patients (100% with NST-ACS)	Benefit of PCI in NSTEMI for elderly patients (mean age 86 years old) with CKD.	Absolute risk of death was 42%, 56%, and 76%, respectively.	OR for in hospital re-IMA: 1.76 (0.71–4.37), 1.89 (0.95–3.76), 3.03 (0.90–10.22), respectively.
		Stratification related to eGFR: >60, 60–30 and <30 mL/min/1.73 m^2.	HR death risk after PCI was lower all groups: 0.47 [95% CI 0.42–0.53], 0.50 [95% CI 0.45–0.56], and 0.44 [95% CI 0.33–0.59], respectively.	OR for in hospital bleeding: 1.62 (0.86–3.08), 1.22 (0.73–2.03), 2.77 (1.03–7.49).
James *et al.* [40], 2010	15,202 (100% with ACS)	Efficacy and safety of ticagrelor vs. clopidogrel in relation to renal function.	In patients with CKD, ticagrelor vs clopidogrel reduced the composite endpoint (CV death, MI and stroke) from 22.0% to 17.3% (HR, 0.77; 95% CI 0.65 to 0.90).	Major bleeding rates, not different (15.1% vs. 14.3%; HR, 1.07; 95% CI 0.88–1.30).
De Filippo *et al.* [41], 2020	19,255 (100% with ACS)	Safety and efficacy profile of prasugrel and ticagrelor in real-life ACS patients with CKD.	Prasugrel and ticagrelor reduced the mortality rate (HR 0.82, 95% CI 0.54–0.96; $p = 0.006$) and the risk of reinfarction (HR 0.53, 95% CI 0.30–0.95; $p = 0.033$) in CKD patients as compared to clopidogrel.	DAPT with either ticagrelor or prasugrel did not result in an increased risk of major bleedings in CKD patients (HR 1.00, 95% CI 0.59–1.68; $p = 0.985$).
Valle McCoy *et al.* [42], 2017	453,475 (66.95% with ACS)	Contrast induced-AKI after PCI, risk and prognosis.	Rate of Contrast induced-AKI was 8.8%.	Re-Hosp for AKI: AKIN 1, HR 1.70 (95% CI 1.64–1.76); AKIN 2/3: HR 2.22 (95% CI 2.04–2.41).
		AKIN stages:	Primary outcome (death, MI, or bleeding within 1 year of hospital discharge):	Dialysis: AKIN 1 HR, 2.59 (95% CI 2.29–2.92); AKIN 2/3 HR, 4.73 (95% CI 3.73–5.99).
		1. as a ≥0.3 mg/dL absolute or 1.5- to 2.0-fold relative increase in sCr;	AKIN 1: HR 1.53; (95% CI 1.49–1.56).	MI: AKIN stage 2/3: HR, 1.29 (95% CI 1.15–1.45); AKIN stage 1 HR 1.32 (95% CI 1.26–1.38).
		2. as a >2- to 3-fold increase in sCr; 3. as a sCr creatinine >4.0 mg/dL with an acute increase of ≥0.5 mg/dL or a >3-fold increase.	AKIN 2/3: HR 2.13; (95% CI 2.01–2.26).	Bleeding: AKIN stage 2/3: HR, 1.40; 95% CI 1.19–1.66; AKIN stage 1: HR, 1.31; 95% CI 1.23–1.40).

In a multicenter, retrospective, observational study from BleeMACS and RENAMI the benefits and safety of potent P2Y12 inhibitors in CKD and ACS patients were investigated. In 19,255 CKD patients (12.9% with eGFR <60 mL/min/1.73 m^2), prasugrel and ticagrelor significantly reduced the mortality rate [HR 0.82, 95% CI 0.54–0.96; p = 0.006] and the risk of reinfarction [HR 0.53, 95% CI 0.30–0.95; p = 0.033] compared to clopidogrel. Potent P2Y12 inhibitors appeared to be safe and did not increase the risk of major bleeding in CKD patients [HR 1.00, 95% CI 0.59–1.68; p = 0.985] [61]. In a subgroup analysis from PLATO trial, patients with renal impairment, defined as eGFR <60 mL/min/1.73 m^2, constituted 21% of those with baseline creatinine measurements, while patients with ESRD requiring dialysis were excluded. Treatment with ticagrelor significantly reduced the primary endpoint (a composite of cardiovascular death, myocardial infarction, and stroke at 1 year) from 22% to 17.3%. No significant increase in major bleeding was reported [60]. Evaluation of this treatment in patients with ESRD are ongoing [41].

In recent years, the attention has been focused on intravenous antiplatelet drugs, which offer a reduction of ischemic events in patients with ACS undergoing PCI. These drugs play a central role extending from perioperative bridging to planned surgery that requires stop of oral P2Y12 antagonist. Two classes of drugs can be defined: glycoprotein IIb/IIIa inhibitors (GPIs) (abciximab, tirofiban, and eptifibatide) and Cangrelor. GPIs block glycoprotein IIb/IIIa receptors on platelet's plasma membrane, preventing the binding of fibrinogen and thus platelet aggregation [31]. Tirofiban and Eptifibatide are renally eliminated and need dosage adjustment if used in patients with CKD. Explicit contraindications exist when used in patients with eGFR less than 15 mL/min/1.73 m^2. On the other hand, tirofiban can be used in stage 4 CKD (eGFR 15 to 30 mL/min/1.73 m^2) with a reduced infusion rate to 50% [62]. Abciximab is not renally eliminated and does not need any adjustments of its dosage for CKD [63]. Several subgroup analyses have confirmed that bleeding is increased in patients who are receiving GPIs and present CKD, especially when the dosage of GPIs is not adjusted for CKD [64]. Cangrelor is the only currently available intravenous platelet P2Y12 receptor inhibitor, with a quickly and reversible platelet inhibition. Cangrelor was approved for patients undergoing PCI for its benefits in reducing ischemic events, including stent thrombosis, and for no detectable increase of major bleeding, versus clopidogrel [65]. Basing on pharmacologic properties [66], cangrelor is indicated in P2Y12 receptor inhibitor-naïve patients undergoing PCI [32] or as bridge therapy in patients undergoing non-cardiac surgery with recent coronary stent. Cangrelor infusion rate is bolus of 30 mcg/kg i.v., followed by a 4 mcg/kg/min infusion for at least 2 hours or until the end of the procedure, if not longer [31]. Since no dose adjustment is required in patients with CKD, cangrelor may be considered as a first choice in patients with ACS and CKD if an intravenous antiplatelet agent is needed during PCI [62].

When administered within the first 24 hours, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are fundamental compounds of post-MI therapy for reducing fatal and nonfatal MACE [61,65]. Nevertheless, evidence is less robust in CKD patients, since there is not a clear cut-off level of sCr that contraindicates the use of these agents [65]. Both ESC and American Heart Association (AHA) STEMI guidelines, state that renal dysfunction should be taken into account as a contraindication for their routine use of ACE-I or ARB [66–71].

There is a paucity of evidence about the use of Sacubitril/Valsartan in patients with CKD and ACS. A recent randomized trial, PARADISE-MI, did not find any statistical significance in MACE rate with the initiation of sacubitril/valsartan therapy vs ramipril in patients with a high risk of heart failure surviving an ACS, regardless of moderate CKD presence (defined as eGFR <60 and >30 mL/min/1.73 m^2) [72].

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) represent a new class of oral hypoglycemic agents used for the treatment of heart failure with reduced ejection fraction, regardless of the presence of DM. To date, evidence about the favorable outcome in CKD patients with ACS treated with SGLT2i is scarce. However, several studies have found a better renal outcome in DM patients with CKD treated with canagliflozin [73] and dapagliflozin [74]. An ongoing study is investigating the use of SGLT2i in DM patients with ACS (ClinicalTrials.gov Identifier: CT0503705; ClinicalTrials.gov Identifier: NCT05037058).

7. Conclusions

A high ischemic risk and rate of AMI occur in CKD patients, with an even higher prevalence in dialyzed patients. Both cardiac and kidney dysfunction may worsen the prognosis and lead to disease progression. Therapeutic strategies employed in ACS can expose CKD patients to higher rates of major and fatal bleeding. This condition leads to an undertreatment attitude and to a conservative approach for patients with renal impairment. Patients with CKD are less frequently treated with percutaneous or surgical revascularization even thought they could potentially benefit from a more invasive management. Moreover, the use of potent P2Y12-ADP antagonists could be considered a significant advantage for CKD patients. Further clinical studies are needed to assess the best treatment strategies for this high-risk subset of patients.

Author contributions

Ethics approval and consent to participate

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Conflict of interest

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